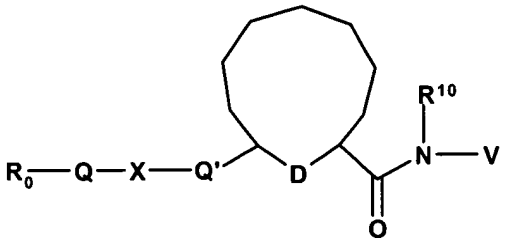
Patent Claims

1. A compound of the formula I,



(I)

wherein

R_0 is
1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2 or
2. a mono- or bicyclic 5- to 10-membered heteroaryl containing one or two nitrogen atoms as ring heteroatoms, wherein heteroaryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2 ,

R^2 is
1. $-NO_2$,
2. halogen,
3. -CN,
4. -OH,
5. $-NH_2$,
6. (C_1-C_8)-alkyloxy-, wherein alkyloxy is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, amino group, hydroxy group or methoxy group, or
7. $-(C_1-C_8)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, amino group, hydroxy group or methoxy group,

Q and Q' are independently of one another identical or different and are a direct bond, -O- , -S- , $-NR^{10}$-, $-C(O)NR^{10}$-, $-NR^{10}C(O)$-, -S(O)-, $-SO_2$-, $-NR^{10}-SO_2$-, $-SO_2-NR^{10}$- oder -C(O)-;

R^{10} is hydrogen atom or (C_1-C_4)-alkyl-,

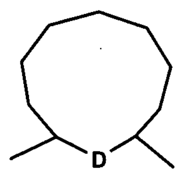
X is
1. a direct bond,
2. (C_1-C_6)-alkylen, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, amino group or a hydroxy group,

3. $(C_3$-$C_6)$-cycloalkylen, wherein cycloalkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, amino group or a hydroxy group,

provided that at least one of Q, X and Q' is not a direct bond,

D is an atom out of the group carbon, oxygen, sulfur and nitrogen,

the substructure of formula III



(III)

is 1. a mono- or bicyclic 5- to 10-membered carbocyclic aryl group, wherein said 5- to 10-membered carbocyclic aryl group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

2. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

3. a mono- or bicyclic 5-to 10-membered heterocyclic group (Het), containing one or more heteroatoms as ring heteroatoms, such as nitrogen, sulfur or oxygen, wherein said Het group is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1 , or

4. pyridyl, wherein pyridyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

R^1 is 1. halogen,

2. $-NO_2$,

3. -CN,

4. $R^{11}R^{12}N$-, wherein $R^{11}R^{12}$ independently of one another are hydrogen atom, $(C_1$-$C_4)$-alkyl- or $(C_1$-$C_6)$-acyl-,

5. $(C_1$-$C_8)$-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

6. -OH,

7. $-SO_2$-NH_2,

8. $(C_1$-$C_8)$-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

9. $(C_6$-$C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

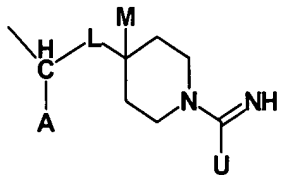
10. (C_1-C_8)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. hydroxycarbonyl-(C_1-C_8)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. (C_1-C_8)-alkyloxycarbonyl-(C_1-C_8)-alkylureido-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
13. (C_1-C_8)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or
14. $-C(O)-NR^{14}R^{15}$, wherein $R^{14}R^{15}$ independently of one another are hydrogen atom or (C_1-C_4)-alkyl-, or

two R^1 residues bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to the ring depicted in formula I, where the ring formed by the two R^1 residues is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

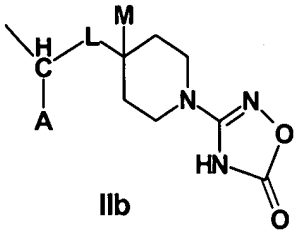
R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5- to 6-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen, and in which one or two of the ring carbon atoms can be substituted by oxo to form -C(O)- residue(s),

R^{13} is
1. halogen,
2. $-NO_2$,
3. -CN,
4. -OH,
5. (C_1-C_8)-alkyl-,
6. (C_1-C_8)-alkyloxy-,
7. $-CF_3$ or
8. $-NH_2$,

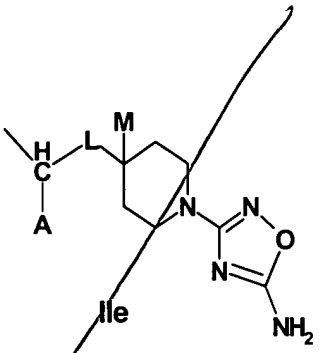
V is a residue of the formulae IIa, IIb, IIc, IId, IIe or IIf,



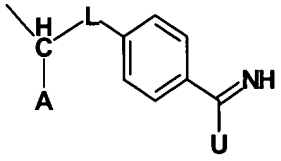
IIa



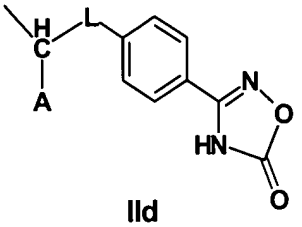
IIb



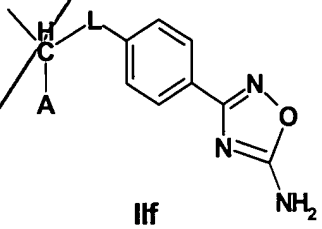
IIe



IIc



IId



IIf

wherein

L is is a direct bond or $(C_1\text{-}C_3)$-alkylene, wherein alkylene is unsubstituted or mono-, di- or trisubstituted independently of one another by A,

A is
1. hydrogen atom,
2. -C(O)-OH,
3. -C(O)-O-$(C_1\text{-}C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or tri- substituted independently of one another by -OH, $-NH_2$ or -$(C_1\text{-}C_4)$-alkoxy,
4. -C(O)-NR^4R^5,
5. $(C_1\text{-}C_4)$-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by -OH, $-NH_2$ or -$(C_1\text{-}C_4)$-alkoxy,
6. $-SO_2\text{-}NH_2$ or
7. $-SO_2\text{-}CH_3$,

U is $-NH_2$, $(C_1\text{-}C_4)$-alkyl-,-NH-C(O)-O-$(C_1\text{-}C_4)$-alkyl or -NH-C(O)-O-$(C_1\text{-}C_4)$-alkyl-aryl,

M is hydrogen atom, $(C_1\text{-}C_3)$-alkyl- or –OH,

R^4 and R^5 are independently of one another identical or different and are

1. hydrogen atom,
2. $(C_1\text{-}C_{12})$-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} as defined above,

3. $(C_6$-$C_{14})$-aryl-$(C_1$-$C_4)$-alkyl-, wherein alkyl and aryl are unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} as defined above,
4. $(C_6$-$C_{14})$-aryl-, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} as defined above,
5. Het-, wherein Het- is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} as defined above, or
6. Het-$(C_1$-$C_4)$-alkyl-, wherein alkyl and Het- are unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13} as defined above, or

R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 3- to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen;

in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

2. A compound of formula I as claimed in claim 1, wherein

R_0 is phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2, or
pyridyl, wherein pyridyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^2,

R^2 is
1. $-NO_2$,
2. halogen,
3. -CN,
4. -OH,
5. $-NH_2$,
6. $(C_1$-$C_4)$-alkyloxy-, wherein alkyloxy is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, amino group, hydroxy group or methoxy group, or
7. $-(C_1$-$C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, amino group, hydroxy group or methoxy group,

Q, Q', X, R^1, R^{11} and R^{12} are as defined in claim 1,

D is an atom out of the group carbon and nitrogen,

the substructure of formula III is

1. phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1, or
2. pyridyl, wherein pyridyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

R^{13} is 1. halogen,
2. $-NO_2$,
3. -CN,
4. -OH,
5. $(C_1\text{-}C_4)$-alkyl-,
6. $(C_1\text{-}C_4)$-alkyloxy-,
7. $-CF_3$ or
8. $-NH_2$,

R_{10} is hydrogen atom or methyl,

V is a fragment of the formula IIa, IIb, IIc, IId, IIe or IIf as defined above, wherein L, U, M, R^4 and R^5 are as defined in claim 1, and

A is 1. hydrogen atom,
2. -C(O)-OH,
3. -C(O)-O-$(C_1\text{-}C_4)$-alkyl, wherein alkyl is unsubstituted or mono-, di- or tri- substituted independently of one another by -OH, $-NH_2$ or $-(C_1\text{-}C_4)$-alkoxy,
4. $-C(O)-NR^4R^5$ or
5. $(C_1\text{-}C_4)$-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by -OH, $-NH_2$ or $-(C_1\text{-}C_4)$-alkoxy.

3. A compound of the formula I as claimed in claims 1 or 2, wherein

R^0 is phenyl, wherein phenyl is mono-, di- or trisubstituted independently of one another by R^2, or
pyridyl, wherein pyridyl is mono-, di- or trisubstituted independently of one another by R^2,

R^2 is 1. $-NH_2$,

2. halogen,
3. -CN,
4. -OH,
5. $(C_1$-$C_4)$-alkyloxy-, wherein alkyloxy is unsubstituted or substituted by an amino group, or
6. -$(C_1$-$C_4)$-alkyl, wherein alkyl is unsubstituted or substituted by an amino group,

Q and Q' are independently of one another identical or different and are a direct bond, -O-, -C(O)NR^{10}-, -NR^{10}C(O)-; -NR^{10}-SO_2-; or -SO_2-NR^{10}-;

X is
1. a direct bond or
2. $(C_1$-$C_4)$-alkylen, wherein alkylen is unsubstituted or mono-, di- or tri-substituted independently of one another by halogen, amino group or a hydroxy group,

D is an atom out of the group carbon and nitrogen,

the substructure of formula III is

phenyl or pyridyl, wherein phenyl and pyridyl are unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

R^1 is
1. halogen,
2. -NO_2,
3. -CN,
4. -NH_2,
5. $(C_1$-$C_4)$-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. -SO_2-NH_2,
8. $(C_1$-$C_4)$-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. $(C_6$-$C_{14})$-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. $(C_1$-$C_4)$-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. $(C_1$-$C_4)$-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

12. -C(O)-$NR^{14}R^{15}$, wherein $R^{14}R^{15}$ independently of one another are hydrogen atom or (C_1-C_4)-alkyl-,
13. $R^{11}R^{12}N$-, wherein R^{11} and R^{12} are as defined above, or
14. -NR^4R^5 ,

R^{13} is 1. halogen,
2. -NO_2,
3. -CN,
4. -OH,
5. (C_1-C_4)-alkyl-,
6. (C_1-C_4)-alkyloxy-,
7. -CF_3 or
8. -NH_2 ,

R_{10} is hydrogen atom or methyl,

V is a fragment of the formula IIa, IIb, IIc, IId, IIe or IIf as defined above, wherein

L is a direct bond or (C_1-C_3)-alkylen-,

A is hydrogen atom, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5 or (C_1-C_4)-alkyl-,

U is -NH_2, methyl, -NH-C(O)-O-(C_1-C_4)-alkyl or -NH-C(O)-O-(CH_2)-phenyl,

M is hydrogen atom, (C_1-C_3)-alkyl- or –OH, and

R^4 and R^5 are independently of one another hydrogen atom or (C_1-C_4)-alkyl-.

4. A compound of formula I as claimed in one or more of claims 1 to 3, wherein

R_0 is phenyl or pyridyl, wherein phenyl and pyridyl independently from one another are mono-, di- or trisubstituted independently of one another by R^2,

R^2 is 1. halogen,
2. -CN,
3. (C_1-C_4)-alkyloxy-, wherein alkyloxy is unsubstituted or substituted by halogen or an amino group, or
4. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted by an amino group or halogen,

Q and Q' are independently of one another identical or different and are a direct bond, -O-, -C(O)NR^{10}-, -NR^{10}C(O)-; -NR^{10}-SO_2-; or -SO_2-NR^{10}-;

X is -(C_1-C_3)-alkylen-, wherein alkylen is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen, amino group or hydroxy group,

D is the atom carbon,

the substructure of formula III is

phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

R^1 is
1. halogen,
2. $-NO_2$,
3. -CN,
4. $-NH_2$,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. $-SO_2-NH_2$,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
9. (C_6-C_{14})-aryl, wherein aryl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
12. $-C(O)-NR^{14}R^{15}$, wherein $R^{14}R^{15}$ independently of one another are hydrogen atom or (C_1-C_4)-alkyl-,
13. $R^{11}R^{12}N$-, wherein R^{11} and R^{12} are as defined above, or
14. $-NR^4R^5$,

R^{13} is
1. halogen,
2. $-CF_3$,
3. $-NH_2$,
4. -OH,
5. (C_1-C_4)-alkyl- or
6. (C_1-C_4)-alkyloxy-,

R_{10} is hydrogen atom, and

V is a fragment of the formula IIa, IIb, IIc or IId as defined above, wherein

L is a direct bond or (C_1-C_2)-alkylen-,

A is hydrogen atom, -C(O)-OH, -C(O)-O-(C_1-C_4)-alkyl, -C(O)-NR^4R^5 or (C_1-C_4)-alkyl,

U is $-NH_2$, methyl, -NH-C(O)-O-(C_1-C_4)-alkyl or -NH-C(O)-O-(CH_2)-phenyl,

M is hydrogen atom or (C_1-C_3)-alkyl-, and

R^4 and R^5 are independently of one another hydrogen atom or methyl.

5. A compound of formula I as claimed in one or more of claims 1 to 4, wherein

R_0 is phenyl, wherein phenyl is mono-, di- or trisubstituted independently of one another by R^2,

R^2 is
1. halogen,
2. (C_1-C_4)-alkyloxy-, wherein alkyloxy is unsubstituted or substituted by halogen or an amino group, or
3. -(C_1-C_4)-alkyl, wherein alkyl is unsubstituted or substituted by an amino group or halogen,

Q and Q' are independently of one another identical or different and are a direct bond, -O-, -C(O)NR^{10}-, -NR^{10}C(O)-; -NR^{10}-SO_2-; or -SO_2-NR^{10}-;

X is -(C_1-C_3)-alkylen-,

D is the atom carbon,

the substructure of formula III is

phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

R^1 is
1. halogen,
2. $-NO_2$,
3. -CN,
4. $-NH_2$,
5. (C_1-C_4)-alkylamino-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
6. -OH,
7. $-SO_2-NH_2$,
8. (C_1-C_4)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

9. (C_1-C_4)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
10. (C_1-C_4)-alkylsulfonyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},
11. $-C(O)-NR^{14}R^{15}$, wherein $R^{14}R^{15}$ independently of one another are hydrogen atom or (C_1-C_2)-alkyl-,
12. $R^{11}R^{12}N-$, wherein R^{11} and R^{12} are as defined above, or
13. $-NR^4R^5$,

R^{13} is 1. halogen,
2. $-CF_3$,
3. $-NH_2$,
4. -OH,
5. (C_1-C_4)-alkyl- or
6. (C_1-C_4)-alkyloxy-,

R_{10} is hydrogen atom, and

V is a fragment of the formula IIa, IIb, IIc or IId as defined above, wherein

L is a direct bond or (C_1-C_2)-alkylen-,

A is hydrogen atom, -C(O)-OH, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$ or $-(C_1-C_4)$-alkyl,

U is $-NH_2$, methyl, $-NH-C(O)-O-(C_1-C_4)$-alkyl or $-NH-C(O)-O-(CH_2)$-phenyl,

M is hydrogen atom or methyl, and

R^4 and R^5 are independently of one another hydrogen atom or methyl.

6. A compound of formula I as claimed in one or more of claims 1 to 5, wherein

R_0 is phenyl, wherein phenyl is disubstituted independently of one another by R^2,

R^2 is 1. halogen,
2. (C_1-C_2)-alkyloxy-, wherein alkyloxy is unsubstituted or substituted by an amino group, or
3. $-(C_1-C_4)$-alkyl, wherein alkyl is unsubstituted or substituted by an amino group,

Q and Q' are independently of one another identical or different and are a direct bond or -O-,

X is $-CH_2-CH_2-$,

D is the atom carbon,

the substructure of formula III is

phenyl, wherein phenyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^1,

R^1 is 1. halogen,

2. -OH,

3. $-NH_2$,

4. $-C(O)-NR^{14}R^{15}$, wherein $R^{14}R^{15}$ independently of one another are hydrogen atom or (C_1-C_2)-alkyl-,

5. (C_1-C_3)-alkyloxy-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13}, or

6. (C_1-C_3)-alkyl-, wherein alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by R^{13},

R^{13} is fluorine or chlorine,

R_{10} is hydrogen atom, and

V is a fragment of the formula IIa, IIb, IIc or IId as defined above, wherein

L is a direct bond or (C_1-C_2)-alkylen-,

A is hydrogen atom, -C(O)-OH, $-C(O)-O-(C_1-C_4)$-alkyl, $-C(O)-NR^4R^5$ or $-(C_1-C_4)$-alkyl,

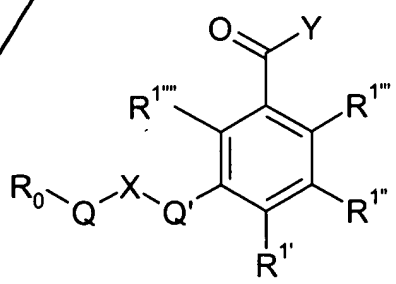
U is $-NH_2$, methyl, $-NH-C(O)-O-(C_1-C_4)$-alkyl or $-NH-C(O)-O-(CH_2)$-phenyl,

M is hydrogen atom, and

R^4 and R^5 are independently of one another hydrogen atom or methyl.

7. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 6, comprises

a) linking a building block of the formula XI,



XI

in which R_0, Q, Q' and X, are as in claims 1 to 6, and $R^{1'}$, $R^{1''}$, $R^{1'''}$, $R^{1''''}$, are hydrogen atom or as R^1 as defined in claims 1 to 6, but where in R_0, Q, R^1, Q' and X functional groups can also be present in protected form or in the form of precursor groups, and Y is a nucleophilically substituable leaving group or a hydroxyl group,

is reacted with a fragment of the formula III

$$H\text{-}NR_{10}\text{-}V \quad (XII)$$

in which R_{10} and V are as defined in claims 1 to 6, but where in R_{10} and V functional groups can also be present in protected form or in the form of precursor groups, or

b) by coupling of a fragment of the formula XIII with fragment XII,

$$R_0\text{-}Q\text{-}X\text{-}Q'\text{-}W\text{-}C(O)\text{-}Y \quad (XIII)$$

in which R_0, Q, Q' and X, are as in claims 1 to 6, W is the substructure of formula III, but where in R_0, Q, Q', W and X functional groups can also be present in protected form or in the form of precursor groups, and Y is a nucleophilically substituable leaving group or a hydroxyl group

or a hydroxy group may be attached to a polystyrene resin.

8. A pharmaceutical preparation , comprising at least one compound of the formula I as claimed in one or more of claims 1 to 6 and/or its physiologically tolerable salts and a pharmaceutically acceptable carrier.

9. The use of a compound of the formula I as claimed in one or more of claims 1 to 6 and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis.

10. The use as claimed in claim 9 for influencing blood coagulation, inflammatory response, fibrinolysis, cardiovascular disorders, thromboembolic diseases, restenoses, abnormal thrombus formation, acute myocardial infarction, unstable angina, acute vessel closure associated with thrombolytic therapy, thromboembolism, percutaneous, pathologic thrombus formation occuring in the veins of the lower extremities following abdominal, knee and hip surgery,

transluminal coronary angioplasty, transient ischemic attacks, stroke a risk of pulmonary thromboembolism, certain viral infections or cancer, intravascular coagulatopathy ocurring in vascular systems during septic shock, coronary heart disease, myocardial infarction, angina pectoris, vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory disstress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder, thromboses like deep vein and proximal vein thrombosis which can occur following surgery.

11. A prodrug of the compound of the formula I as claimed in claims 1 to 6, preferably a (C_1-C_6)-acyl or (C_1-C_6)-alkyloxycarbonyl prodrugs of the compound of the formula I as claimed in claims 1 to 6.